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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/748,374	Applicant(s) SU, XING
	Examiner Katherine Salmon	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 22-36* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-18 and 22-32, drawn to a method to determine a nucleotide sequence of a target nucleic acid and determining a nucleotide occurrence at a target nucleotide position of a template nucleic acid, classified in class 435, subclass 6.

   II. Claims 19-21, drawn to a detection system comprising a Raman spectrometer, a Raman active surface, a population of Raman-active oligonucleotide probes, and a biochip, classified in class 435, subclass 287.2.

   III. Claims 33-36, drawn to a method for detecting a nucleic acid comprising irradiating the nucleic acid with light and detecting a Raman signal, classified in class 435, subclass 6The inventions are distinct, each from the other because of the following reasons:

2. Inventions II and (I and III) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the detection system could be used in a method of determining a nucleotide sequence or a method of

detecting a nucleic acid, but the detection station could also be used in a method of detecting expression levels. The search for each invention presents a serious burden, as the searches for each are not coextensive in scope. Art relating to the methods of detecting differential modulation of a gene would not necessarily provide descriptive sequence information of the polymorphism itself, and vice versa.

2. Inventions I and III are distinct methods. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the groups are drawn to distinct methods, which have different goals and modes of operations. The methods share a common step wherein they utilize a Raman-active oligonucleotide. Beyond this commonality, however, the methods are distinct from one another because they have different goals and would require different additional process steps, reagents, and analyses for their completion.

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance,

whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter and because Inventions I-III require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Lisa Haile on 2/06/2006 a provisional election was made with traverse to prosecute the invention of I, claims 1-18 and 22-32. Affirmation of this election must be made by applicant in replying to this Office action.

7. After review of the claims requirement for restriction of Groups I and III has been withdrawn. The requirement for restriction is withdrawn between Groups I and III and Claims 1-18 and 22-36 have been rejoined.

8. Claims 19-21 are withdrawn from consideration.

Abstract

9. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology

often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract begins with the wording, “provided herein” which is implied. Correction is required. See MPEP § 608.01(b).

Specification

10. The disclosure is objected to because of the following informalities: there is a patent number missing in a reference (p. 8 paragraph 28).

Appropriate correction is required.

Claim Objections

11. Claim 5 is objected to because of the following informalities: a period needs to be placed at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 5-7, 9-10, 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Cao et al. (Science August 2002 Vol 297 p. 1536).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Claim 16) (Abstract). With regard to Claim 1 and 15, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column).

With regard to Claim 5, Cao et al. teaches the use of an AU nanoparticle modified with Cy3-labeled, alkylthiol-capped oligonucleotide strands as probes. These probes would be a composite of organic-inorganic nanoparticles.

With regard to Claims 6 and 7, Cao et al. teaches a method of determining the nucleotide position at of a SNP in a bound target sequence (p. 1539 Figure 4). With regard to Claim 9, Cao et al. teaches a method in which the target sequence is less than the combined length of the capture probe and the Raman-active probe (p. 1539 Figure 4). With regard to Claim 10, the claim is broadly interpreted to define the length of the Raman-active oligonucleotide probe as the "entire" probe length. Cao et al. teaches the probe is comprised of 110 oligonucleotide strands on an Au nanoparticle (p. 1537 2nd paragraph 1st column). It is inherent in the teaching that the combined length of the 110 oligonucleotide strands would be greater than the target probe length.

With regard to Claim 13, the methods of Cao et al. are conducted in the absence of an amplification step.

With regard to Claim 14, Cao et al. teaches a method in which each spot on the microarray is a target: capture probe duplex (abstract). Cao et al. teaches that at least one Raman dye label can be used as a probe, therefore Cao et al. teaches the limitation of 1000 or less molecules of Raman-active probes detected (p. 1537 Figure 1).

With regard to Claim 17, Cao et al. teaches a method of labeling nanoparticles with 6 different dyes and contacting each of the Raman probes to a different probe:target duplex on the array (p. 1538 Figure 2). With regard to Claim 18, Cao et al. teaches a method in which eight tests were performed using the 6 target:probe complexes in which a mixture of different Raman probes was added to the sandwich assay and each Raman SERS spectra for each Raman probe was determined (p. 1538 1st column last paragraph and 2nd paragraph near the bottom). Each complex had more

than one Raman-active probe bound to the substrate and each Raman-active probe could be detected.

14. Claims 22-25 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002).

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

With regard to Claim 24 and 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

With regard to Claim 29, Bruchez, Jr. et al. teaches the method can be used in minisequencing methods, detecting mutations (nucleotide occurrences) (p. 3 paragraph 39). Bruchez, Jr. et al. teaches SNPs can be detected (p. 3 paragraph 39). Bruchez, Jr. et al. teaches the method for SNP detection can be multiplexed (p. 3 paragraph 41). Bruchez, Jr. et al. teaches one or more different populations can be blended together so that more than one population can be assayed at the same time (p. 3 paragraph 42). Bruchez, Jr. et al. teaches a multiplex methods in which different probe polynucleotides can be used simultaneously with corresponding different target polynucleotides (p. 3 paragraph 43).

15. Claims 33-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Vo-Dinh (US Patent 6,174,677 January 16, 2001).

Vo-Dinh teaches a method of using SER (surface enhanced Raman)-labeled gene probes for hybridization, detection, and identification of SER-labeled hybridized target oligonucleotides (Abstract). With regard to Claim 33, Vo-Dinh teaches that SER labels are bound to different target oligonucleotide strands (Column 9, lines 27-61). Vo-Dinh teaches using a Raman spectrometer to determine signal detection of the labeled targets (Column 21 lines 58-60). Vo-Dinh teaches using a photomultiplier tube operated in the photon counting mode (irradiating the nucleic acid with light). With regard to claim 34, Vo-Dinh teaches the use of aminoacridine as a SER label (e.g. a positively-charged enhancer) (Column 9, lines 27-61). With regard to Claim 35, it is inherent in the teaching that if the aminoacridine is not attached to the nucleic acid then a signal will not be generated.

With regard to Claim 36, the instant specification does not limit the nucleic acid to only pyrimidine residues. The examples in the instant specification are oligonucleotides, which include pyrimidine residues, but are not only pyrimidine residues (p. 42 paragraph 148). Vo-Dinh teaches a method in which the target is DNA (Column 7, lines 43-44). DNA is composed of pyrimidines and purines therefore would be encompassed by the limitation of Claim 36.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS Raman probes (Abstract). With regard to Claim 1, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target: capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column).

Cao et al., however, does not specifically mention other Raman probes, which could be used in the method of SNP sequencing.

Cao et al. teaches another method of determining if multiple dyes could be used in a multiplex method (p. 1538 1st column 1st full paragraph). With regard to Claims 2-4

Cao et al. teaches one of the Raman probes that can be used is Rhodamine (e.g. an anime).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of SNP sequencing of Cao et al. to further include the use of other dyes such as Rhodamine. The ordinary artisan would have been motivated to use various Raman probes because Cao et al. teaches different Raman dyes can be used to label different oligonucleotide sequences (p. 1537 1st column 1st paragraph). The ordinary artisan would be motivated to use various types of labels to be able to multiplex the reaction for the obvious improvement of testing more than one SNP at a time.

17. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) in view of Lane et al. (US Patent 5,770,365 June 23, 1998).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS Raman probes (Claim 16) (Abstract). With regard to Claim 1 and 15, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a

signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column).

Cao et al., however, does not teach a method in which the capture probe and the oligonucleotide probe are ligated.

Lane et al. teaches a method of using nucleic acid capture moieties to detect nucleic acid sequences (Column 4, lines 19-25). Lane et al. teaches a labeled probe complementary to a target-complementary region of the capture moiety that is immobilized on insoluble support (Column 11, lines 30-35). With regard to Claim 12, Lane et al. teaches a method in which the detectable probe is ligated to the capture probe (a duplex-binding ligand binding site) (Figure 3).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. to further include the use ligated probes as taught by Lane et al. The ordinary artisan would have been motivated to improve the method of Cao et al. because Lane et al. teaches that the ligation method can be used for the detection of nucleic acid sequences, which do not occur near the terminus of an intact target strand (Column 12, lines 15-20).

17. Claims 1, 5-11 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Research July 2000 Vol. 10(7) p. 1031) in view of Cao et al. (Science August 2002 Vol 297 p. 1536).

Pastinen et al. teaches a method of genotyping by allele-specific primer extension on a microarray (abstract). With regard to Claim 1 and 15, Pastinen

et al. teaches a method in which a primer (probe) is attached to a microarray (Figure 1). Pastinen et al. teaches that a target is bound to the primer in which there is a region of single-strand (Figure 1). Pastinen et al. teaches that label dNTPs are then used to extend the probe-target complex and detection via fluorescence can be made at the 3' end (figure 1). With regard to Claim 6 and 7, Pastinen et al. teaches a method of genotyping single nucleotide polymorphisms (SNPs) (a nucleotide occurrence) using an allele specific primer extension on a microarray (Abstract).

With regard to Claim 8, Pastinen et al. teaches that the array can be composed of a multiplex of mutations (p. 1033 1st column last sentence and second column 1st paragraph). Pastinen et al. teaches a multiplex method of PCR followed by genotyping on microarrays (p. 1033 2nd column 1st paragraph). Pastinen et al. teaches a microarray composed of PCR reactions each drawn to a mutation of a target sequence (p. 1033 2nd column 1st paragraph). If you are targeting occurrences of a nucleotide it is inherent that the targeting would be the detection of nucleotide occurrences of a target segment.

It is obvious in the teaching that an array can be composed of probes wherein each probe is used to determine the nucleotide of each adjacent basepair.

With regard to Claim 11, Pastinen et al. teaches genotyping in which using primer extension a user can determine the sequence of the extended target (Abstract). Pastinen et al. teaches using a array of a multiplex of primers each specifically near a SNP area of detections (p. 1033 1st column last sentence and second column 1st paragraph). It is obvious in the teaching that a user can make an

array composes of probes that when extended can detect nucleotides. After detection of the nucleotide from each primer extension the complete sequence of the target could be determining by aligning the nucleotides from each probe.

Pastinen et al., however, does not teach using Raman probes instead of labeled dNTPs to determine the sequence identity.

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS Raman probes (Claim 16) (Abstract). With regard to Claim 1 and 15, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column).

With regard to Claim 5, Cao et al. teaches the use of an AU nanoparticle modified with Cy3-labeled, alkylthiol-capped oligonucleotide strands as probes. These probes would be a composite of organic-inorganic nanoparticles.

With regard to Claims 6 and 7, Cao et al. teaches a method of determining the nucleotide position at of a SNP in a bound target sequence (p. 1539 Figure 4).

With regard to Claim 9, Cao et al. teaches a method in which the target sequence is less than the combined length of the capture probe and the Raman-active

probe (p. 1539 Figure 4). With regard to Claim 10, the claim is broadly interpreted to define the length of the Raman-active oligonucleotide probe as the "entire" probe length. Cao et al. teaches the probe is comprised of 110 oligonucleotide strands on an Au nanoparticle (p. 1537 2nd paragraph 1st column). It is inherent in the teaching that the combined length of the 110 oligonucleotide strands would be greater than the target probe length.

With regard to Claim 14, Cao et al. teaches a method in which each spot on the microarray is a target: capture probe duplex (abstract). Cao et al. teaches that at least one Raman dye label can be used as a probe, therefore Cao et al. teaches the limitation of 1000 or less molecules of Raman-active probes detected (p. 1537 Figure 1).

With regard to Claim 17, Cao et al. teaches a method of labeling nanoparticles with 6 different dyes and contacting each of the Raman probes to a different probe:target duplex on the array (p. 1538 Figure 2). With regard to Claim 18, Cao et al. teaches a method in which eight tests were performed using the 6 target:probe complexes in which a mixture of different Raman probes was added to the sandwich assay and each Raman SERS spectra for each Raman probe was determined (p. 1538 1st column last paragraph and 2nd paragraph near the bottom). Each complex had more than one Raman-active probe bound to the substrate and each Raman-active probe could be detected.

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Pastinen et al. to further include the use of Raman probes as taught by Cao et al. The ordinary artisan would be

motivated to improve the method of Pastinen et al. because Cao et al. teaches a method of using Raman probes which would allow multiplex sequencing. The ordinary artisan would want to use Raman probes because Cao et al. teaches that Raman dyes can be used to label different oligonucleotides to distinguish oligonucleotide sequences (p. 1537 1st column 1st paragraph). The ordinary artisan would be motivated to use many probes with a variety of dyes in order to provide for multiplexing that would allow for the detection of an increased number of SNPs simultaneously.

18. Claims 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) in view of Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS Raman probes (Claim 16) (Abstract). With regard to Claim 1, 15, and 26, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column).

With regard to Claim 27, Cao et al. teaches a method that uses a multiple color scanning Raman method in which more than one label can make up each spot (p. 1538 2nd column). It is obvious to one skilled in the art that to determine the frequencies of each labeled used in the multiplex method one would need to look up the published spectra readings to determine which labels are incorporated in spot.

Cao et al., however, does not teach using probes that have a first and second signal attached.

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

With regard to Claim 24 and 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. to further include the use of Hairpin probes. The ordinary artisan would have been motivated to improve the method of Cao et al. because Bruchez et al. teaches a method particularly useful in multiplex settings where a plurality of different conjugates are used to assay for a plurality of different target polynucleotide and the large number of distinguishable

semiconductor nanocrystal labels allows for simultaneous analysis of multiple labeled target polynucleotide (p. 2 paragraph 16).

19. Claims 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002) in view of Livak et al. (US Patent 5,723,591 March 3, 1998) as evidenced by DNA from Wikipedia.com.

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

With regard to Claim 24 and 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

Bruchez, Jr. et al., however, does not teach the distance the quencher and reporter should be apart on the probe strand.

Livak et al. teaches that the quencher molecule and reporter should be between 6-16 nucleotides (Column 3, line 63). As evidenced by Wikepedia.com the distance between nucleotides is 0.23 nm, therefore the distance between a reporter and quencher can be between 1.38 to 3.68 nm apart (between 3-6 nm).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bruchez, Jr. et al. to

further include distance limitation as taught by Livak et al. The ordinary artisan would have been motivated to improve the method of Bruchez, Jr. et al. because Livak et al. teaches that there is a distance that must be maintained between the quencher and reporter in order for the quencher to be able to quench the reporter in the assay (Column 3, lines 60-65).

20. Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002) and in view of Chan et al. (US Patent Application Publication March 27, 2003).

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

With regard to Claim 29, Bruchez, Jr. et al. teaches the method can be used in minisequencing methods (p. 3 paragraph 39). A minisequencing method would be used to determine the nucleotide at each position of a target sequence using a population of probes.

Bruchez, Jr. et al., however, does not teach reading each nucleotide as it passes through a channel optically.

Chan et al. teaches a method for spatial resolution of signal detection (Abstract). With regard to Claim 30, Chan et al. teaches a method of passing a target through an optical detector to read florescent signals (p. 12 paragraphs 114 and 115). With regard to Claim 31, Chan et al. teaches an interactor station comprised of the channel and the optical detector (e.g. a microelectromechical system) (p. 12 paragraph 115). With regard to Claim 32, Chan et al. teaches that the target nucleotide is pulled through the nanoslit of the channel by applying an alternating current filed to the metal layer (p. 14 paragraph 132).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bruchez Jr. et al. to further include the use of a channel, optical detector, and AC current as taught by Chan et al. The ordinary artisan would have been motivated to improve the method of Bruchez Jr. et al. to include the channel, optical detector, and AC current taught by Chan et al. because Chan et al. teaches a method of linear analysis of DNA which can allow for the development of specific sequences to be used in sequence-specific tagging (p. 1 paragraph 3 and 4).

Conclusion

21. No claims allowable over the cited prior art.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday -Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Katherine Salmon 2/17/2006
Katherine Salmon
Examiner
Art Unit 1634

Jehanne Sitton
JEHANNE SITTON
PRIMARY EXAMINER
2/17/06